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ORIGINAL ARTICLE

Synthesis, anti-tuberculosis activity and QSAR study of 2,4-diarylquinolines and analogous polycyclic derivatives

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QSAR

Abstract The multicomponent syntheses of 2,4-*di*-aryl-quinolines and analogous polycyclic derivatives as *anti*-tuberculosis agents were described. They were prepared *via* Beyer and Friedländer methods under microwave irradiation in short reaction times and good yields. Several homogeneous and heterogeneous acid catalysts were compared for preparing 2,4-*di*-arylquinolines and among them trifluoroacetic acid (TFA) reached the higher yields. Two derivatives exhibited activity against *Mycobacterium tuberculosis* H37Rv (*Mtb*), underwent additional testing and were considered lead compounds. The synthesis of a series of polycyclic analogous led to six new active compounds and a Quantitative Structure Activity Relationship study (QSAR) study was established.

1. Introduction

Tuberculosis (TB) is caused by bacteria (*Mycobacterium tuberculosis*) that most often affect the lungs. In 2016, an estimated 1 million children became ill with TB and 250,000 children died of TB (including children with HIV associated TB). Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. WHO estimates that there were 600,000 new cases with resistance to rifampicin, the most effective first-line drug, of which 490,000 had MDR-TB. Ending the TB epidemic by 2030 is among the health targets of the newly adopted Sustainable Development Goals. By June 2017, 89

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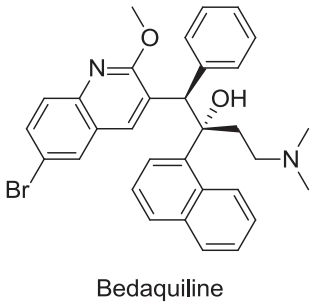
countries had introduced bedaquiline and 54 countries had introduced delamanid (a dihydro-nitroimidazooxazole derivative), in an effort to improve the effectiveness of MDR-TB treatment regimens (Tuberculosis Fact sheet, WHO, 2018).

Bedaquiline, previously known as TMC207 (Fig. 1), was developed by Johnson & Johnson pharmaceutical company. This diarylquinoline (DARQ) acts by a novel mechanism by targeting proton pump of adenosine triphosphate (ATP) synthesis, leading to inadequate synthesis of ATP (Andries et al., 2005; Rustomjee et al., 2008). A quinoline moiety is its essential pharmacophoric feature and the bedaquiline performance encouraged several authors for the design and synthesis of new drugs (Tanwar et al., 2016). The quinoline alkaloids 4-methoxy-2-phenylquinoline, graveolinine and kokusagine isolated from *Lunasia amara*, showed significant activity towards *M. tuberculosis* $H_{37}Rv$ *in vitro* (Metallidis et al., 2007). More recently, new 4-substituted quinoline derivatives of the anti-malarial drug mefloquine exhibited *anti*-tuberculosis properties (Eswaran et al., 2010). Furthermore 2-substituted quinolines isolated from plants or prepared by synthesis, have exhibited activity against leishmaniasis (Fournet et al., 1996; Gopinath et al., 2014), Chagas disease (Muscia et al., 2011) and *M. tuberculosis* (Jain et al., 2003; Patel et al. 2014, 2015). The quinoline ring was shown to confer anti-TB activity and confirms that quinoline-based scaffolds are promising leads for new TB drug developments (Casal and Asís, 2017) as depicted in Fig. 2 for our previously synthesized quinolines A-C (Muscia et al., 2014). We have also reported the microwave-assisted Döbner synthesis of 2-phenylquinoline-4-carboxylic acids and their activities against malaria, trypanosomiasis and leishmaniasis (Muscia et al., 2008). The parent compound 2-phenyl-4-quinolincarboxylic acid **4** (Atophan) and its analogous **5**, **6**, **7** and **8**, were further evaluated for growth inhibitory activity towards *M. tuberculosis* $H_{37}Rv$ (*Mtb*) through the National Institute of Allergy and Infectious Diseases (NIAID, USA) and showed no activity (Scheme 1, A). Since 2-styrylquinoline-4-carboxylic acids had not been sufficiently explored as anti-TB agents and thus the effect of a vinyl group, we have synthesized a series of ten derivatives. Only the compounds featuring the 3,5-*di*-OCH_3-phenyl, 3,4-methylendioxyphenyl and 1-naphthyl moieties attached at the C2 of vinyl group showed weak activity against *M. tuberculosis* under aerobic conditions (Muscia et al., 2017). Thus the analogous 2-aryl-4-quinolin-carboxylic acids **9**–**11** and **14** were prepared (Scheme 1, A and B). Although these four derivatives had been already reported, their NMR spectra were not described. Moreover, compound **9** with a 1-naphthyl ring attached at C2 was cited for the treatment of TB (Tsatsas



Bedaquiline

Fig. 1 Chemical structure of bedaquiline.

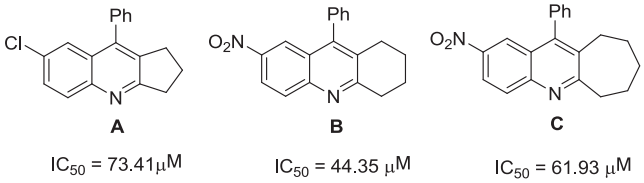


Fig. 2 Lead fused quinolines **A-C.**

et al., 1955) but these data are not available. Later, the family of DARQ **16**–**23** was prepared *via* the Beyer method, another multicomponent reaction (MCR), with the aim to analyze the effect of introducing a second aryl moiety at C4 of the quinoline ring (Scheme 2).

Finally, the DARQ series was extended to the polycyclic and fused quinolines **26**–**45** analogous to our lead compounds (Schemes 3 and 4). A computational analysis of the different molecular descriptors for each product was performed in order to establish a Quantitative Structure Activity Relationship (QSAR) study.

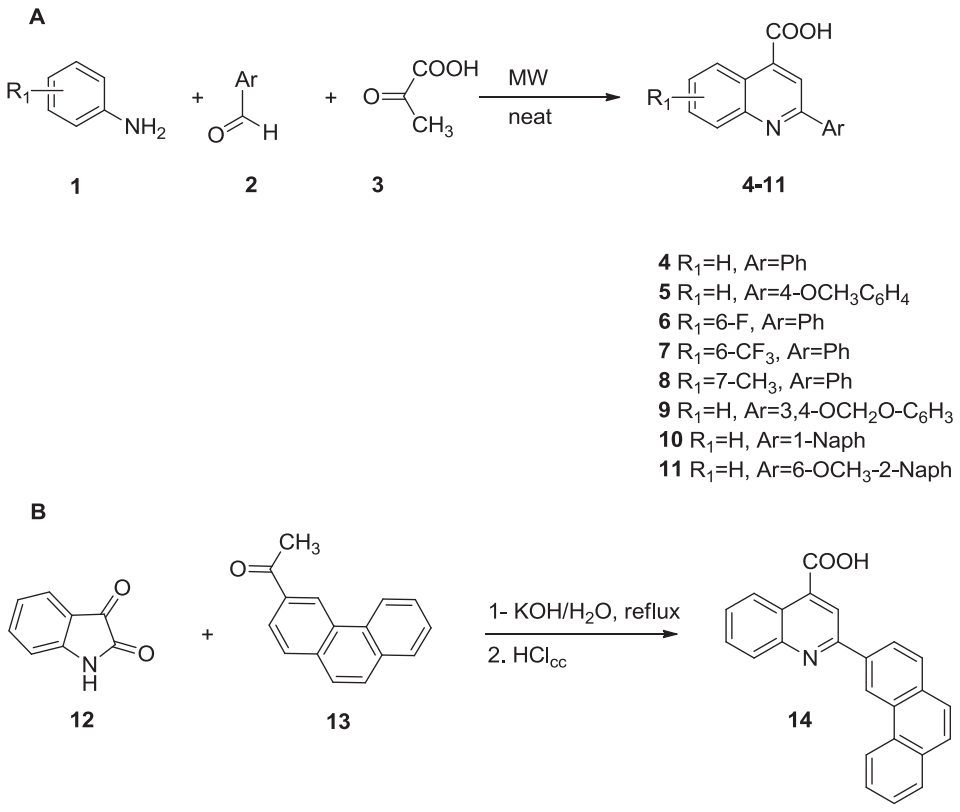
2. Results and discussion

2.1. Chemistry

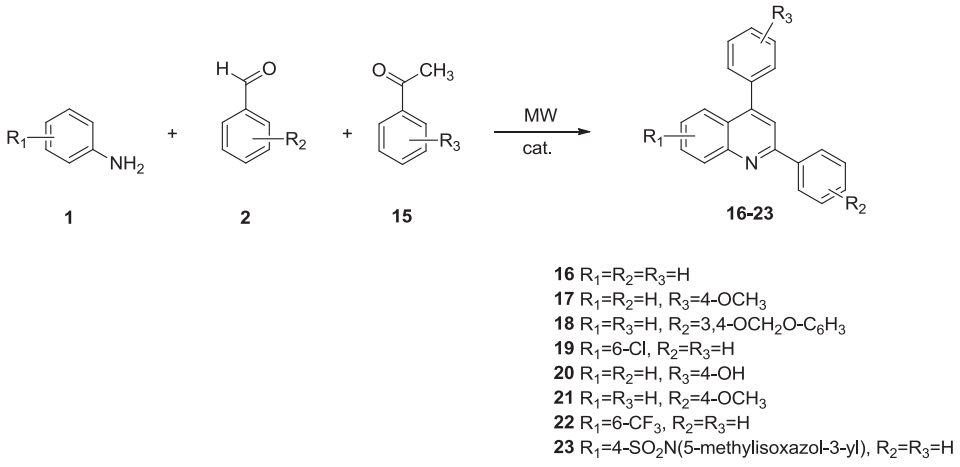
The microwave-assisted Döbner reaction from substituted anilines (**1**), arylaldehydes (**2**) and pyruvic acid (**3**) was employed to prepare 2-aryl-4-quinoline carboxylic acids **9**–**11**, (Scheme 1, A) (Muscia et al., 2008). Although the yields of this MCR are poor, it is worthy to use in order to achieve in short reaction times a wide variety of substituted quinolines from easily affordable starting materials. Furthermore, this work showed that microwave irradiation (MW) improved all yields compared to two-hour thermal heating. To complete this first series, the Pfitzinger reaction (Pfitzinger, 1886) from isatine (**12**) and 3-acetyl-phenanthrene (**13**) was used to afford compound **14** (Scheme 1, B).

In order to determine the effect on the anti-TB activity of a second aryl moiety attached at position 4 of the quinoline, the pyruvic acid of Döbner synthesis was replaced for a variety of methyl aryl ketones (**15**) maintaining the same neat reaction conditions (Scheme 2). Therefore, 2,4-diarylquinolines **16**–**23** were obtained *via* the microwave assisted one-pot Beyer method (Beyer, 1886), as a modification of the Döbner-Miller reaction. Owing to the low yields, the addition of homogeneous catalysts, trifluoroacetic acid (TFA) and Eaton's reagent (Eaton et al., 1973), and heterogeneous catalysts (sulfamic acid (H_2NSO_3H) and Amberlyst® 15) was evaluated. The reaction times and yields for compounds **16**–**23** are shown in Table 1. TFA catalysis proved to be more effective as long as the yields were between 35 and 89% and the reactions times were within 1.5–9 min. Whereas for compounds **21** and **22**, Eaton's reagent and no catalyst, respectively, exhibited the best performances.

A variety of synthetic methods have been developed to obtain 2,4-disubstituted quinolines. In this regard, 2,4-diarylquinolines were prepared by reactions of *o*-isocyano-*β*-methoxystyrenes with nucleophiles, from 2-iodoanilines and alkynyl aryl ketones, Silver-catalyzed cascade reaction of *o*-aminoaryl compounds with alkynes, among others. The synthesis of compounds **16** (Tanwar et al., 2016; Kobayashi

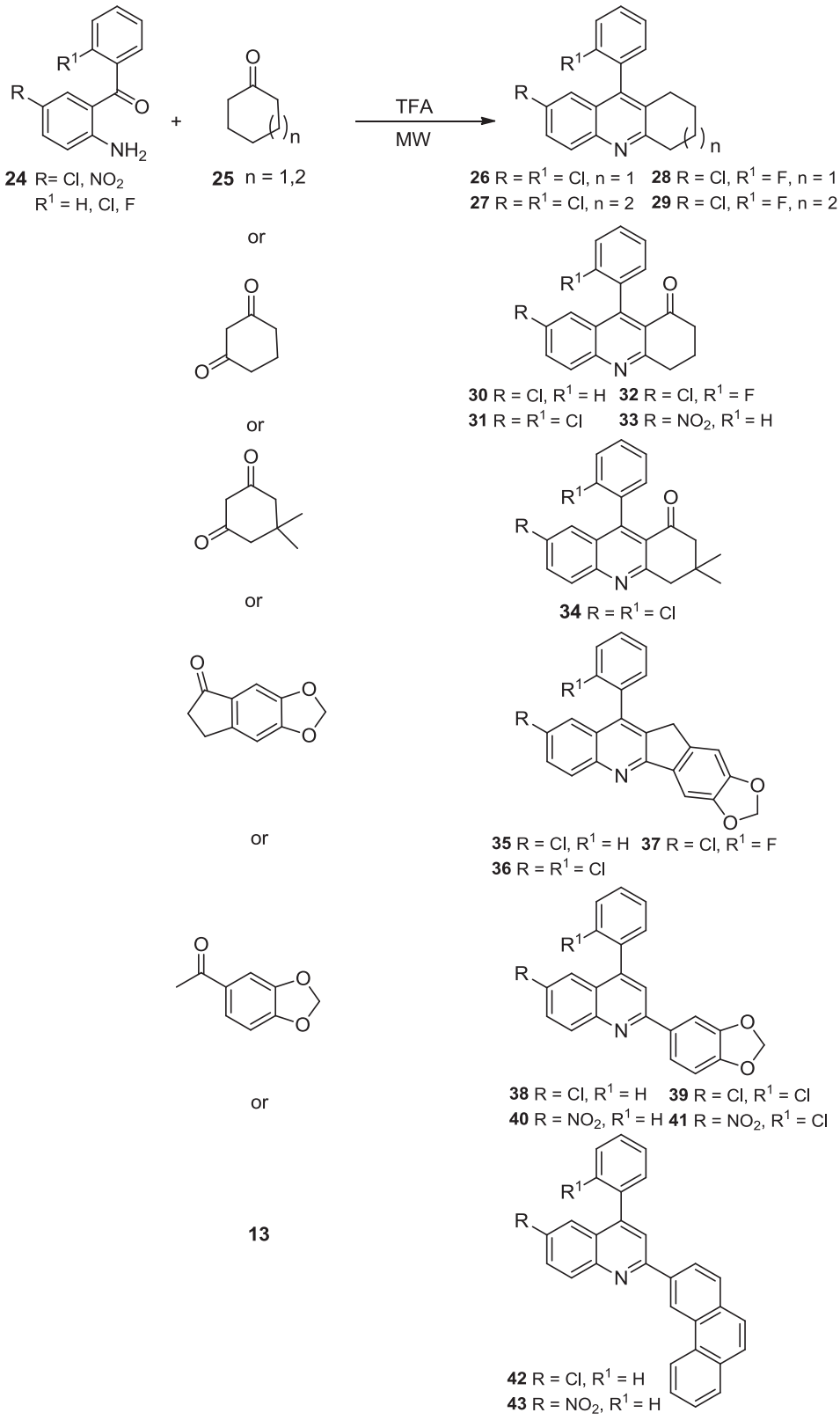


Scheme 1 Synthesis of 2-aryl-4-quinolincarboxylic acids **4**–**11** and **14** *via* Döbner and Pfitzinger reactions.



Scheme 2 Synthesis of 2,4-DARQ **16**–**23** *via* Beyer method.

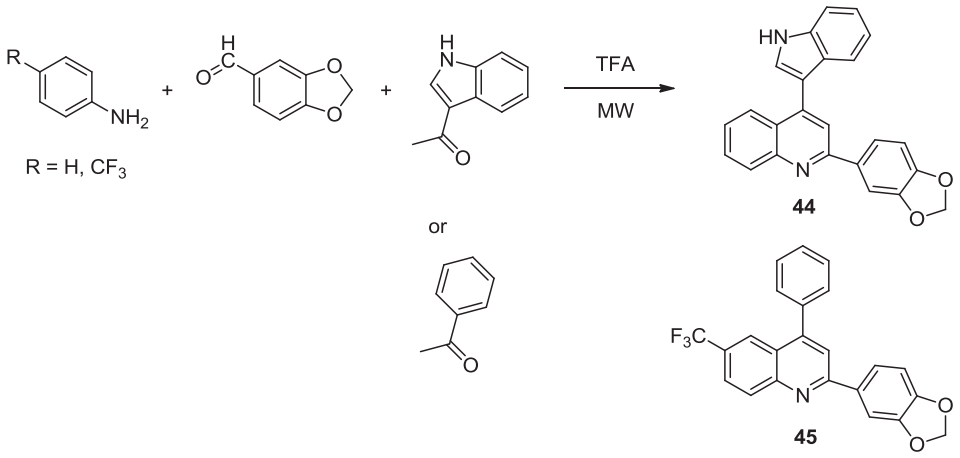
et al., 2004; Prasad Korivi and Cheng, 2006; Tang et al., 2011; Li et al., 2011; Zhang et al., 2013; Xu et al., 2016), **17** (Ahmad et al., 2012), **19** (Kobayashi et al., 2004; Tang et al., 2011; Palimkar et al., 2003; Rehan et al., 2015; Muscia et al., 2006), **21** (Tang et al., 2011; Zhang et al., 2013; Enugala et al., 2008) and **22** (Xu et al., 2016; Rehan et al., 2015) were reported by these or other two-steps methods involving long reaction times and expensive reagents or by MCR with high-priced catalysts. Recently, compounds **16**, **19** and **22** were obtained in comparable yields to our work, *via* MW-assisted Povarov reaction in the presence of *p*-sulfonic acid calix[4] arene (CX_4SO_3H) as catalyst (Liberto et al., 2017). The synthesis of compound **18** was found as a progress report from the reaction of 2-vinylaniline and piperonal after 15 h in refluxing toluene and 40% yield, and its melting point and NMR spectra were not given (Walter, 1998). Compounds **20** and **23** have not been previously described. The last one possesses a 4-sulfona mido-5-methylisoxazol-3-yl substituent at C6 position and



Scheme 3

was prepared from sulfamethoxazole, a recognized antimicrobial agent and thus a pharmacophore moiety for anti-TB activity (Aly, Abadi, 2004).

The above described experimental conditions support that the MW-assisted Beyer method for the synthesis of 2,4-diarylquinolines promoted by TFA is a rapid, neat and versa-



Scheme 4 Synthesis of quinoline derivatives **44** and **45** *via* Beyer method.

Table 1 Preparation of compounds **16–23** with acid catalysts.

Compd	No Catalyst		TFA		Eaton's		H_2NSO_3H		Amberlyst® 15	
	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Rto (%)	Time (min)	Yield (%)
16	6	63	9	89	10	43	6	19	5	19
17	20	30	3	56	3	13	4	50	nr	–
18	6	< 10	2.5	44	1	26	2	24	5	< 10
19	3	49	1.5	76	14	35	3	49	3	13
20	4	18	5	52	2	24	4	27	2	< 10
21	10	13	5	12	6	37	6	32	1	11
22	6.5	38	2	< 10	2	30	2	< 10	2	< 10
23	6	< 10	4	35	3	20	2	< 10	2	< 10

tile reaction that can be extended to a large variety of 2,4-diarylquinolines successfully prepared in short times.

Taking into account the remarkable anti-TB activity results for compounds **14** and **18** (Section 2.2.1) and considering our former lead fused quinolines **A-C** (Fig. 2), the analogous **26–43** were synthesized employing MW-assisted Friedländer reaction (Scheme 3) (Muscia et al., 2014) and **44–45** through the Beyer method (Scheme 4), both under TFA catalysis.

The tetrahydroacridine derivative **26** was prepared in 2015 using a tandem process that involves *in situ* aerial oxidation of the corresponding alcohol followed by Friedländer annulation in the presence of KOH at 80 °C for 7 h (Anand et al., 2015). Recently was reported the water mediated green Friedländer synthesis of the polycyclic quinolines **28–32** and **34** under diluted HCl catalysis at room temperature. Although the authors obtained comparable yields to ours, the reactions proceeded in longer reaction times (Gopi and Sarveswari (2017)). Finally the 4-indolylquinoline derivative **44** was cited by Chen et al. in 2015 in a process that involves two steps, the Michael addition of indole to a nitrochalcone followed by a reductive cyclization of the indolylnitrochalcone intermediate.

The spectroscopical analysis of our products agrees with the reported data. All our synthesized quinoline derivatives were obtained in short reaction times under *eco*-friendly conditions, ease of purification and the ready availability of the starting materials. These advantages are imperative for designing biological active compounds.

2.2. Biological activity

2.2.1. In vitro activity against M. Tuberculosis

Initially the 2-aryl-4-quinoline carboxylic acids **9–11**, **14** and DARQ **16–23** were evaluated for growth inhibitory activity towards *M. tuberculosis* $H_{37}Rv$ (*Mtb*) through the National Institute of Allergy and Infectious Diseases (NIAID, USA) and rifampicin was used as reference drug (NIH/NIAID Task Order A01 Contract HHSN272201100012I).

Compounds **14**, **18** and **19** exhibited IC_{50} values of 60.25, 29 and 19 μM, respectively but only compounds **14** (2-phenanthren-3-yl) and **18** 2-(3,4-methylenedioxyphenyl) underwent additional testing and are also considered lead compounds. This subset was determined by an algorithm that considered primarily activity and analytical quality of the samples but also considered other aspects such as chemotype series and solubility. This testing includes *in vitro* evaluation of $H_{37}Rv$ under both anaerobic and aerobic conditions as well as minimal bactericidal concentration (MBC). Single drug resistant strain testing (isoniazid, rifampicin and ofloxacin resistant *Mtb* strains) and intracellular inhibition of *Mtb* $H_{37}Rv$ growth using murine macrophage cell line and cytotoxicity in this cell-line were also determined.

The twenty derivatives **26–45** designed as analogous of lead compounds **A-C**, **14** and **18** (Schemes 3 and 4) were evaluated against *Mtb* using rifampicin as reference drug (MIC 0.0072 μM) and six of them showed inhibitory activity

(Table 2). The additional halogen atom (Cl or F) attached at C2 of the 4-phenyl moiety in compounds **26**–**29** did not improve the IC_{50} values of **A**-**C**. The chlorine atom at C6 of quinoline ring in compound **38** conferred less activity meanwhile the trifluormethyl group increased the activity comparing to the lead **18** however it was not selected for additional testing. The polycyclic quinolines **35**–**37** as constrained models of **18** lacked of activity as well as the 2-phenanthryl derivatives **42** and **43** analogous to **14** (Fig. 3).

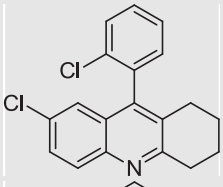
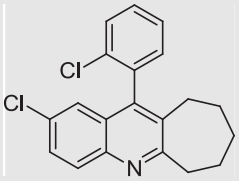
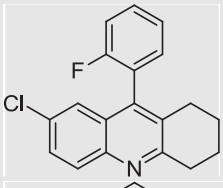
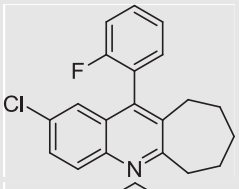
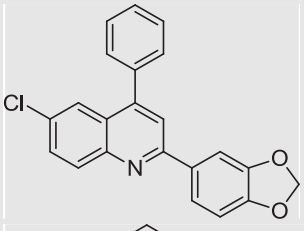
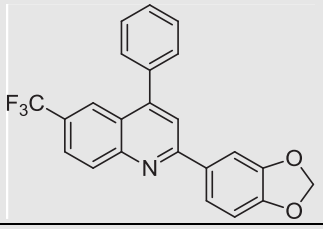
2.2.2. Minimal inhibitory concentration (MIC)

The MIC for each compound was determined by testing ten, two-fold dilutions in concentration ranges. The MIC is reported as the lowest concentration (μM) of drug that visually inhibited growth of the organism. In addition, the percentage of inhibition at the MIC is provided for compound **14** (Table 3). Rifampicin and isoniazid were used as positive controls. Although MIC values of compound **14** were higher than the MIC values for the reference drugs, this compound showed a similar percent inhibition value against the rifampicin resistant strain (RMP-R) and a higher percent inhibition value against the ofloxacin resistant strain (OFX-R). On the other hand, compound **18** had limited activity against *M. tuberculosis* resistant.

2.2.3. Minimal bactericidal concentration (MBC)

The established rejection value of >40 colonies for the MBC assay was based on the calculated concentration of *Mtb* in

Table 2 In vitro activity against *M. tuberculosis* $H_{37}Rv$ of analogous active compounds.

Compd	Structure	IC_{50} (μM)	IC_{90} (μM)	MIC (μM)
26		81	158	>200
27		65	97	102
28		130	190	200
29		95	>200	>200
38		162	>200	>200
45		21	118	73

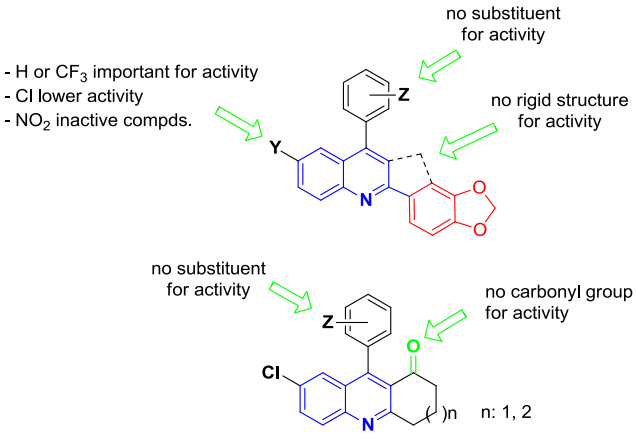


Fig. 3 SAR of the synthesized quinolines.

the MIC plates. Results are determined based on Colony Forming Units (CFUs) enumerated from agar plates. Only agar plates with countable colonies have reportable counts. If a compound lacks bactericidal activity, many times the CFUs are too numerous to count (TNTC) and are thus reported as such. This result was the one obtained for compound **14**, meanwhile compound **18** proved bactericidal activity so far the MBC value was 100 μM.

2.2.4. Low-oxygen recovery assay (LORA)

Traditional screening of drugs against *M. tuberculosis* only addresses or targets the organism in an active replicating state. It is well documented that *Mtb* can reside in a state of non-replicating persistence (NRP) which has not been adequately assessed in the development of new antimicrobials. Results for the LORA assay are reported as the lowest concentration of drug that visually inhibited growth of the organism. This NRP state is considered an antimicrobial tolerance factor, so LORA may identify drugs that could reduce anti-tubercular treatment period. Compound **14** exhibited higher MIC value under anaerobic than under aerobic conditions. Compound **18** had activity against *M. tuberculosis* under low oxygen conditions and the MIC, IC_{50} and IC_{90} values were 136, 7.3 and 30 μM, respectively.

2.2.5. Intracellular drug activity

Intracellular drug activity is reported as log reduction values calculated as reduction in Mtb concentration from zero hour to 7 days post-infection. The three concentrations chosen were based on the MIC data generated in the HTS primary screen. The mid concentration bracketed the reported MIC with the lower concentration ten-fold below the mid and the higher concentration tenfold above the mid. Drug cytotoxicity is reported as cell proliferation, macrophage toxicity (MTT) or percentage of viability. Compound **14** showed a similar tendency as rifampicin, so at higher drug concentrations lower UFC are obtained and the log reduction is higher (Table 4). Concerning cytotoxicity, compound **14** exhibited percentages of viability comparable to rifampicin at low and mid concentrations, so it is not toxic to macrophages. Compound **18** had intracellular activity against *M. tuberculosis* and was cytotoxic (IC_{50} = 82 μM).

2.3. QSAR study

The analogous compounds **26**–**29**, **38** and **45** have been classified as 'active' and the remaining structures as 'inactive'. All the active molecules have pIC_{50} values above 4.22 log units. The molecules were built with ChemAxon Marvin Sketch 6.0 and exported to MOL2 format. A total of 1444 1D and 2D different molecular descriptors were calculated using PaDEL-Descriptor v2.7, Table 5 (Todeschini and Consonni, 2009). Descriptors with zero standard deviation in their values were then removed. The principal component analysis (PCA) showed that three principal components (PC) explained 97% of the variance in the chemical structure. The first three PCA vectors were added to the study table containing the binary representation of the activity of the molecules (Tables 6 and 7). Summarizing, PC1 is related to the number of aromatic bonds, PC2 with the effect and position of the substituents and PC3 with the molecular distances between atoms and the tertiary quinoline nitrogen.

3. Conclusion

We herein describe the multicomponent, *eco*-friendly synthesis of 31 quinoline derivatives in short reaction times and

Table 3 Percentage of inhibition at the MIC for compound **14.**

Comp	MIC $H_{37}Rv$ (μM)	% Inhib[a]	MBC $H_{37}Rv$ (μM)	MIC INH-R[b] (μM)	% Inhib	MIC RMP-R[c] (μM)	% Inhib	MIC OFX-R[d] (μM)	% Inhib
14	25.1	60	NA[e]	12.6	50	25.1	62	6.28	77
Rifampicin (pos control)	0.06	57	0.95	0.06	68	NA[f]	NA	0.47	63
Isoniazid (pos control)	NA	NA	NA	NA	NA	0.15	74	NA	NA

[a] Percent inhibition at the MIC concentration.
[b] INH-R: Isoniazid Resistance.
[c] RMP-R: Rifampicin Resistance.
[d] OFX-R: Ofloxacin Resistance.
[e] NA: Not Applicable, Colony Counts above the established rejection value of ≥40.
[f] NA: Not Applicable, Compound not used in assay.

Table 4 Macrophage toxicity (MTT) and percentage of viability of compound **14.**

Comp.	Macrophage log reduction (low conc)	Macrophage log reduction (mid conc)	Macrophage log reduction (high conc)	MTT % viability (low conc)	MTT % viability (mid conc)	MTT % viability (high conc)
14	1.56	1.98	2.54	100	100	80
Rifampicin	0.58	2.00	2.98	90	79	82

Table 5 Calculated molecular descriptors for compounds **26–45.**

Compd	AMR	nHBAcc	nHBDon	nRing	nRotB	Ro5 Failures	TPSA	MW	XLogP
26	26.37	1	0	4	1	1	12.89	327.058	6.380
27	29.28	1	0	4	1	1	12.89	341.073	6.949
28	21.62	1	0	4	1	1	12.89	311.087	6.243
29	24.54	1	0	4	1	1	12.89	325.103	6.812
30	23.3	3	0	6	1	1	31.35	405.032	6.098
31	21.14	5	0	4	2	1	73.10	318.100	5.846
32	39.5	2	0	4	1	1	29.96	369.068	6.210
33	23.74	2	0	4	1	0	29.96	325.066	4.959
34	3.89	4	0	6	3	1	56.03	426.136	12.668
35	11.36	6	0	5	3	1	74.49	370.095	7.322
36	16.97	6	0	5	3	1	74.49	404.056	6.363
37	22.87	2	0	4	1	1	29.96	307.076	6.055
38	13.08	3	0	5	2	1	31.35	359.071	7.531
39	18.7	3	0	5	2	1	31.35	393.032	6.572
40	5.615	1	0	6	2	1	12.89	415.112	12.877
41	28.48	2	0	4	1	1	29.96	341.037	5.096
42	17.68	3	0	6	1	1	31.35	371.071	7.057
43	10.77	4	1	6	2	1	47.14	364.121	6.034
44	13.96	3	0	5	2	1	31.35	377.061	6.435
45	13.9	3	0	5	3	1	31.35	393.097	8.549

Table 6 Eigenvectors for the first components.

Principal Component	VR2Dt[a]	nBondsM[b]	nAtomP[c]	MDEC-23[d]	nssCH2[e]	nwHBa[f]	C2SP2[g]
PC1	0.1087	**0.5011**	0.456	0.5194	−0.1219	0.3972	0.2942
PC2	**0.9873**	−0.0316	0.0092	−0.1446	−0.0257	−0.0413	−0.0246
PC3	−0.1108	0.0458	0.5291	**−0.7276**	−0.3088	0.0126	0.2825

Major contribution property values to each PC are depicted in bold.
[a] Normalized Randic-like eigenvector-based index from detour matrix.
[b] Total number of bonds that have bond order greater than one.
[c] Number of atoms in the largest pi system.
[d] Molecular distance edge between all secondary and tertiary nitrogens.
[e] Count of atom-type E-State: $-CH_2-$.
[f] Minimum E-States for weak Hydrogen Bond acceptors.
[g] Doubly bound carbon bound to two other carbons.

from easily affordable starting materials and their anti-TB activity. Among the synthesized compounds, fifteen are novel structures and the remaining terms have been reported in the literature although prepared by other experimental conditions and from different expensive starting materials. All products were evaluated *in vitro* against *M. tuberculosis* (*Mtb*) $H_{37}Rv$. Nine compounds showed inhibitory activity and compounds **14** and **18** underwent additional testing. Compound **18** had limited activity against *M. tuberculosis* resistant, proved to be bactericidal and had activity against *M. tuberculosis* under low oxygen conditions, although was cytotoxic. By contrast, compound **14** had a higher percent inhibition value against the ofloxacin resistant strain (OFX-R), lacked of bactericidal activity, was not active under low oxygen conditions and exhibited percentages of viability comparable to rifampicin at low and mid concentrations, so it was not toxic to macrophages. Considering the established minimal structural requirements supported by theoretical calculations, it is worthy to note that the introduction of a sulfonamide moiety at C6 of the quinoline ring in future series could improve the anti-TB activity and diminish the cytotoxicity.

Table 7 Principal components for each tested compound.

Compound	PC1	PC2	PC3
26	−11.534	−3.415	−1.432
27	−10.755	−3.2	−2.983
28	−11.534	−3.415	−1.432
29	−10.755	−3.2	−2.983
30	4.005	−1.841	−1.331
31	−7.314	−0.285	1.867
32	−9.959	1.55	1.858
33	−9.305	−2.506	0.313
34	24.349	−4.6	−1.443
35	4.53	−2.449	4.007
36	5.31	1.178	3.073
37	−7.459	15.38	−1.526
38	2.649	−2.554	2.386
39	3.433	1.112	1.447
40	22.488	−4.523	−3.086
41	−9.305	−2.506	0.313
42	4.483	2.426	−1.824
43	10.869	14.144	−0.758
44	3.433	1.112	1.447
45	2.368	−2.408	2.087

4. Experimental section

4.1. Chemistry

The structures of the synthesized compounds were established through their ^{1}H and ^{13}C NMR, MS and IR spectra. Melting points were determined in a capillary Electrothermal 9100 SERIES-Digital apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at room temperature using a Bruker 300 spectrometer. The operating frequencies for protons and carbons were 300.13 and 75.46 MHz, respectively. When indicated, the spectra were obtained using a Bruker 600 spectrometer. The operating frequencies for protons and carbons were 600 and 151 MHz, respectively. The chemical shifts (δ) were given in ppm. IR spectra were recorded on an FT Perkin Elmer Spectrum One from KBr discs. Mass spectra were measured on MS/DSQ II Thermo Scientific DIP or Agilent MSD, electrospray ionization, positive ion. Elemental analysis (C, H and N) were performed on an Exeter CE 440 and the results were within ±0.4% of the calculated values. Analytical TLCs were performed on DC-Alufolien Kieselgel 60 F_{254} Merck. Microwave-assisted reactions were carried out in a CEM Discover oven.

4.1.1. 2-Arylquinoline-4-carboxylic acids

*4.1.1.1. General procedure for compounds **9**–**11**.* A mixture of the corresponding aniline (0.37 mL, 4.1 mmoles), arylaldehyde (0.58–0.73 g, 3.9 mmoles) and pyruvic acid (0.30 mL, 4.3 mmoles) placed in a 50 mL round-bottomed flask was subjected to MW irradiation at 400 W and 250 °C. After completion of the reaction (TLC), the reaction mixture was allowed to cool and the residual semisolid crystallized. When this did not occur, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with water, 5% HCl (10 mL) and brine (10 mL). This was then dried (Na_2SO_4) and concentrated *in vacuo* to give a solid product (Muscia et al., 2008).

4.1.1.2. 2-(3,4-methylenedioxyphenyl)quinoline-4-carboxylic acid 9. White solid; yield 45%, mp 215–218 °C, crystallized from EtOH. ^{1}H NMR (DMSO d_6): δ 6.13 (s, 2H, OCH_2O), 7.08 (d, J = 8.1 Hz, 1H, H-Ph), 7.66 (1H, t, Het-H), 7.79–7.85 (2H, m, Ph-H and Het-H), 7.87 (1H, s, Ph-H), 8.11 (1H, d, J = 8.5 Hz, Het-H), 8.39 (1H, s, Het-H), 8.59 (1H, d, J = 8.5 Hz, Het-H). ^{13}C NMR (DMSO d_6): δ 101.63 (OCH_2O), 107.05, 108.68, 118.81, 121.84, 123.29, 125.33, 127.40, 129.64, 130.19, 132.24, 137.63, 148.26, 149.08, 155.21 (C_{arom}), 167.7 (COOH). 101.6, 107.0, 108.6, 118.8, 121.8, 123.2, 125.3, 127.4, 129.6, 130.1, 132.2, 137.6, 148.2, 149.0, 155.2, 167.7. IR (cm^{-1}): υ 3392, 3004, 1715, 1264, 1036, 764, 690. MSD 292 (M^+).

Anal. Calcd. for $C_{17}H_{11}NO_4$: C, 69.62; H, 3.78; N, 4.78. Found: C, 69.58; H, 3.72; N, 4.81.

4.1.1.3. 2-(naphthalen-1-yl)quinoline-4-carboxylic acid 10. Pale yellow solid; yield 25%, mp 170 °C d, Lit. 198 °C (Buu-Hoï, 1943), crystallized from cyclohexane. ^{1}H NMR (DMSO d_6): δ 7.46–7.47 (2H,m, Ph-H), 7.61 (1H, t, Het-H), 7.66 (1H, t, Ph-H), 7.71 (1H, t, Het-H), 7.83–7.87 (2H, m, Ph-H), 7.93 (1H, d, J = 8.2 Hz, Ph-H), 8.13 (1H, d, J = 7.9 Hz, Ph-H), 8.20 (1H, s, Het-H), 8.25 (1H, d, J = 7.7 Hz , Het-H), 8.51 (1H, d, J = 7.7 Hz, Het-H). ^{13}C NMR (DMSO d_6): δ 122.9, 125.2, 125.3, 125.5, 125.8, 126.6, 126.7, 127.1, 127.9, 130.0, 130.8, 131.0, 134.5, 143.6, 149.3, 157.7(C_{arom}), 171.2 (COOH). IR (cm^{-1}): υ 3314, 3044, 1678, 1397, 779, 719. MS (EI): MSD 297 (M^+).

Anal. Calcd. for $C_{20}H_{13}NO_2$: C, 80.25; H, 4.38; N, 4.68. Found: C, 80.21; H, 4.44; N, 4.60.

4.1.1.4. 2-(6-methoxynaphthalen-2-yl)quinoline-4-carboxylic acid 11. Orange solid; yield 25%, mp 149–151 °C, Lit. 258–259 °C (Buu-Hoï, 1949), crystallized from cyclohexane. ^{1}H NMR (DMSO d_6): δ 3.9 (3H, s, OCH_3), 7.21–7.29 (3H, m, Ph-H), 7.39–7.45 (3H, m, Ph-H), 7.92 (2H, t, Het-H), 8.07 (1H, d, J = 8.7 Hz, Het-H), 8.30 (1H, d, J = 8.7 Hz, Het-H), 8.69 (1H, s, Het-H). ^{13}C NMR (DMSO d_6): δ 55.3 (OCH_3), 106.3, 113.8, 115.6, 119.3, 120.9, 124.2, 125.7, 127.5, 127.9, 130.3, 131.1, 131.6, 136.1, 151.6, 158.7, 159.8 (C_{arom}), 160.5 (COOH). IR (cm^{-1}): υ 3468, 3002, 1689, 1477, 1032, 758, 694. MSD 119.1 (M^+).

Anal. Calcd. for $C_{21}H_{15}NO_3$: C, 76.58; H, 4.59; N, 4.25. Found: C, 76.54; H, 4.57; N, 4.28.

*4.1.1.5. 2-(phenanthren-3-yl)quinoline-4-carboxylic acid **14**.* A mixture of 3.4 mmoles (0.5 g) of isatine and 7.1 mmoles (1.5 g) of 3-acetyl-phenanthrene in 20 mL 20% KOH was stirred at reflux temperature for 7 h. The reaction mixture was cooled to rt and concd HCl was added to pH 6.5 and the crystalline solid was filtered and crystallized from *i*-PrOH.

White solid; yield 54%, mp 261–263 °C, Lit. 268 °C (Buu-Hoï, 1943). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70–7.80 (3H, m), 7.90–7.96 (3H, m), 8.04 (1H, d, J = 7.8 Hz), 8.19 (1H, d, J = 8.3 Hz), 8.30 (1H, d, J = 8.3 Hz), 8.62 (2H, t), 8.83 (1H, s), 9.13 (1H, d, J = 8.2 Hz), 9.68 (1H, s). ^{13}C NMR (151 MHz, $CDCl_3$): δ 120.0, 122.5, 123.8, 125.8, 126.1, 126.9, 127.6, 127.7, 128.4, 128.7, 129.1, 129.7, 130.0, 130.4, 130.5, 130.9, 132.3, 133.1, 136.4, 138.9, 148.5, 156.3 (C_{arom}), 168.2 (COOH). IR (cm^{-1}): υ 3435, 3065, 1717, 1630, 1589, 847, 717. MSD 349 (M^+).

Anal. Calcd. for $C_{24}H_{15}NO_2$: C, 82.50; H, 4.33; N, 4.01. Found: C, 82.53; H, 4.31; N, 3.98.

4.1.2. Diarylquinolines (DARQ)

4.1.2.1. General procedure for compounds ***16–23***. A mixture of the corresponding aniline (0.51–1.39 g, 5.5 mmoles), arylaldehyde (0.55–0.79 g, 5.25 mmoles), substituted acetophenone (0.66–0.82 g, 5.5 mmoles) and 1% of catalyst placed in a 50 mL round-bottomed flask was subjected to MW irradiation at 400 W and 250 °C. After completion of the reaction (TLC), the reaction mixture was allowed to cool. It was diluted with CH_2Cl_2 (15 mL) and washed with water, 5% HCl (10 mL) and brine (10 mL). This was then dried (Na_2SO_4) and concentrated *in vacuo* to give a solid product which was crystallized from the corresponding solvent. The yields are shown in Table 1.

4.1.2.2. 2-(3,4-methylenedioxyphenyl)-4-phenylquinoline ***18***. Pale yellow solid, mp 149–151 °C, crystallized from cyclohexane. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.05 (2H, s), 6.87 (1H, d, J = 6.9 Hz), 7.15 (1H, d, J = 8.0 Hz), 7.19 (1H, s), 7.20 (1H, s), 7.39 (1H, d, J = 15.5 Hz), 7.52 (2H, t), 7.60 (1H, t), 7.76 (1H, d, J = 15.5 Hz), 8.03 (2H, d, J = 8.1 Hz). ^{13}C NMR (151 MHz, $CDCl_3$): δ 101.6 (OCH_2O), 106.7, 108.7, 120.1, 125.2, 128.4, 128.6, 129.4, 132.6, 138.4, 144.7, 148.4, 149.9 (C_{arom}). IR (cm^{-1}): υ 3062, 2913, 1674, 1456, 1260, 804, 717. MS (EI): 325 (M^+), 252 (100%), 122 (21%), 77 (26%).

Anal. Calcd. for $C_{22}H_{15}NO_2$: C, 81.21; H, 4.65; N, 4.30. Found: C, 81.23; H, 4.63; N, 4.34.

4.1.2.3. 4-(4-hydroxyphenyl)-2-phenylquinoline ***20***. White solid, mp 174–175 °C, crystallized from CH_2Cl_2. ^{1}H NMR ($CDCl_3$): δ 6.57–6.62 (3H, m), 6.68 (2H, d, J = 8.2 Hz), 6.69 (1H, s), 7.15 (2H, d, J = 7.9 Hz), 7.35 (1H, s), 7.42 (2H, d, J = 8.1 Hz), 7.83 (2H, d, J = 7.9 Hz), 7.79 (2H, d, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$): δ 116.8, 119.8, 122.5, 124.8, 125.5, 126.9, 129.8, 130.0, 131.2, 132.6, 143.7, 146.2, 147.8 (C_{arom}), 159.8 (C_{arom}-OH). IR (cm^{-1}): υ 3300, 3010, 1594, 1485, 1283, 834, 751, 699. MS (EI): 297 (M^+), 182 (100%), 121 (36%), 93 (50%), 77 (22%).

Anal. Calcd. for $C_{21}H_{15}NO$: C, 84.82; H, 5.08; N, 4.71. Found: C, 84.79; H, 5.10; N, 4.67.

4.1.2.4. 2,4-diphenyl-6-(4-sulfonamido-5-methylisoxazol-3-yl) quinoline ***23***. White solid, mp 222–223 °C, crystallized from EtOH. ^{1}H NMR (DMSO d_6): δ 2.51 (3H, s), 6.07 (1H, s), 6.59 (2H, d, J = 8.8), 7.67–7.20 (10*H*, m), 7.98 (2H, d, J = 7.2 Hz), 10.94 (1H, s). ^{13}C NMR (DMSO d_6): δ 12.5 (CH_3), 112.1, 125.2, 127.0, 127.5, 128.5, 128.9, 129.1, 133.7, 137.1, 143.4 (C_{arom}). IR (cm^{-1}): υ 3369, 3283, 3109, 3065, 1674, 1587, 1174, 1087, 760, 696. MS (EI): 442 (M^+), 207 (100%), 162 (31%), 92 (32%), 77 (24%).

Anal. Calcd. for $C_{25}H_{19}N_3O_3S$: C, 68.01; H, 4.34; N, 9.52. Found: C, 68.05; H, 4.31; N, 9.55.

4.1.3. Polycyclic quinolines

4.1.3.1. General procedure for compounds ***26–43***. A neat mixture of 1.00 mmol of 2-amino-5-chlorobenzophenones (0.23–0.27 g) or 2-amino-5-nitrobenzophenones (0.24–0.28 g) **24** and 1.50 mmol of the corresponding cyclanone or methylketone (0.15–0.26 g) **25** with 0.15 mL TFA was subjected to MW irradiation, at 400 W and 250 °C. The completion of the reaction was determined by TLC (Muscia et al., 2014). The product was crystallized from EtOH and the reaction times were 2–6 min.

4.1.3.2. 2-chloro-11-(2-chlorophenyl)-7,8,9,10-tetrahydro-6H-cyclohepta[b]quinoline ***27***. White solid, yield 63%, mp 151–153 °C, crystallized from EtOH. ^{1}H RMN (600 MHz, $CDCl_3$): δ 1.56–1.72 (m, 2H, CH_2), 1.87 (s, 4H, CH_2), 2.58–2.70 (m, 2H, CH_2), 3.26–3.33 (m, 2H, CH_2), 7.10 (s, 1H, H-Het), 7.19 (dd, J = 1.4; J = 7.3 Hz, 1H, H—Ar), 7.41–4.48 (m, 2H, H—Ar), 7.56 (dd, J = 2.2; J = 8.9 Hz, 1H, H—Ar) 7.60 (d, J = 7.8 Hz, 1H, H—Ar), 7.99 (d, J = 8.9 Hz, 1H, H-Het).^{13}C NMR (151 MHz, $CDCl_3$): δ 26.9 (CH_2), 27.8 (CH_2), 30.9 (CH_2), 31.9 (CH_2), 40.2 (CH_2), 124.4, 127.1, 129.2, 129.7, 129.9, 130.4, 131.0, 131.7, 133.7, 135.2, 135.8, 141.8, 144.3, 165.1 (C_{arom}). IR (cm^{-1}): υ 3044, 2918, 2841, 1575, 1468, 1169, 829, 757. MSD 342 (M^+).

Anal. Calcd. for $C_{20}H_{17}Cl_2N$: C, 70.18; H, 5.01; N, 4.09. Found: C, 69.85; H, 4.96; N, 4.11.

4.1.3.3. 7-nitro-9-phenyl-3,4-dihydroacridin-1(2H)-one ***33***. Yellow solid; yield 35%, mp 195–197 °C, crystallized from EtOH. ^{1}H RMN ($CDCl_3$): δ 2.25–2.37 (m, CH_2, 2H), 2.78 (t, CH_2, J = 6.7 Hz, 2H), 3.44 (t, CH_2, J = 6.2 Hz, 2H), 7.19–7.23 (m, 2H, H-Ph), 7.54–7.59 (m, 3H, H-Ph), 8.21, (d, J = 9.2 Hz, 1H, H-Het), 8.44 (s, 1H, H-Het), 8.53 (d, J = 9.2 Hz, 1H, H-Het). ^{13}C NMR ($CDCl_3$): δ 21.0 (CH_2), 34.8 (CH_2), 40.5 (CH_2), 124.9, 125.0, 125.3, 126.8, 128.0, 128.5, 130.5, 145.6, 150.5, 153.2, 166.1 (C_{arom}), 197.1 (C═O). IR (cm^{-1}): υ 3000, 2890, 1696, 1616, 1554, 1338, 714, 688. MSD 113.1 (M^+).

Anal. Calcd. for $C_{19}H_{14}N_2O_3$: C, 71.69; H, 4.43; N, 8.80. Found: C, 71.47; H, 4.50; N, 8.50.

4.1.3.4. 8-chloro-10-phenyl-11H-[1,3]dioxolo[4′,5′:5,6]indeno[1,2-b]quinoline ***35***. Pale yellow solid; yield 55%, mp 254–256 °C, crystallized from EtOH. ^{1}H RMN (600 MHz, $CDCl_3$): δ 3.72 (s, 2H, CH_2), 6.08 (s, 2H, OCH_2O), 6.93 (s, 1H, H-Ph), 7.45 (d, J = 7.0 Hz, 2H), 7.54–7.62 (m, 5H, H—Ar), 7.7 (s, 1H, H-Het), 8.12 (d, J = 9.6 Hz, 1H, H-Het).

^{13}C NMR (151 MHz, $CDCl_3$): δ 33.80 (CH_2), 101.69 (OCH_2O), 101.9, 105.5, 124.6, 126.6, 128.5, 128.9, 129.0, 129.2, 129.4, 130.4, 130.9, 134.1, 134.2, 135.8, 140.5, 142.0, 146.8, 148.1, 150.4, 161.2 (C_{arom}). IR (cm^{-1}): υ 3000, 2900, 1566, 1468, 1331, 1259, 1037, 833, 708. MSD 372.0 (M^+).

Anal. Calcd. for $C_{23}H_{14}ClNO_2$: C, 74.30; H, 3.80; N, 3.77. Found: C, 74.69; H, 3.89; N, 3.55.

4.1.3.5. 8-chloro-10-(2-chlorophenyl)-11H-[1,3]dioxolo[4′,5′:5,6]indeno[1,2-b]quinoline ***36***. Pale yellow solid; yield 60%, mp 250–251 °C, crystallized from EtOH. ^{1}H RMN (600 MHz, $CDCl_3$): δ 3.68 (q, 2H, CH_2), 6.10 (s, 2H, OCH_2O), 6.96 (s, 1H, H—Ar), 7.35–7.38 (m, 2H, H-Ph), 7.48–7.54 (m, 2H, H-Ph), 7.63–7.66 (m, 2H, H—Ar), 7.73 (s, 1H, H-Het), 8.15 (d, J = 8.9 Hz, 1H, H-Het). ^{13}C NMR (151 MHz, $CDCl_3$): δ 33.5 (CH_2), 101.7 (OCH_2O), 102.0, 105.6, 124.2, 126.4, 127.2, 129.6, 130.1, 130.5, 130.8, 131.2, 133.3, 134.1, 134.9, 139.3, 140.4, 146.7, 148.2, 150.5, 161.2, 165.4 (C_{arom}). IR (cm^{-1}): υ 3062, 2925, 2847, 1755, 1471, 1428, 1170, 829, 759. MSD 406.0 (M^+).

Anal. Calcd. for $C_{23}H_{13}Cl_2NO_2$: C, 68.00; H, 3.23; N, 3.45. Found: C, 67.88; H, 3.17; N, 3.38.

4.1.3.6. 2-(benzo[d][1,3]dioxol-5-yl)-6-chloro-4-(2-fluorophenyl)quinoline ***37***. Pale yellow solid; yield 50%, mp 133–135 °C, crystallized from EtOH. ^{1}H RMN (600 MHz, $CDCl_3$): δ 6.04 (s, 2H, OCH_2O), 6.86 (d, J = 8.4 Hz, 1H, H—Ar), 7.44–7-52 (m, 3H, H—Ar), 7.61–7.68 (m, 2H, H—Ar), 7.81 (dd, J = 2.3 Hz, J = 9.0 Hz, 1H, H-Ph),7.93 (d, J = 5.5 Hz, 2H, H-Het), 8.16 (d, J = 8.7 Hz, 2H, H-Het). ^{13}C NMR (151 MHz, $CDCl_3$) δ 101.6, 106.7, 108.7, 120.1, 125.2, 128.4, 128.6, 129.4, 132.6, 138.4, 144.7, 148.4, 149.9 (C_{arom}). IR (cm^{-1}): υ 3067, 2897, 2775, 1592, 1481, 1446, 1251, 1038, 873, 764. MSD 378.0 (M^+).

Anal. Calcd. for $C_{22}H_{13}ClFNO_2$ C, 69.94; H, 3.47; N, 3.71. Found: C, 70.04; H, 3.50; N, 3.67.

4.1.3.7. 2-(benzo[d][1,3]dioxol-5-yl)-6-chloro-4-phenylquinoline ***38***. Pale yellow solid; yield 61%, mp 142–144 °C, crystallized from EtOH. ^{1}H RMN (DMSO d_6): δ 6.12 (s, 2H, OCH_2O), 7.08 (d, J = 8.1 Hz, 1H, H—Ar), 7.50–7.63 (m, 5H, H—Ar), 7.73 (d, J = 2.0 Hz, 1H, $H_3C_6OCH_2O$), 7.80 (dd, J = 2.1 Hz; J = 8.9 Hz; 1H, $H_3C_6OCH_2O$), 7.92 (d, J = 6.3 Hz, 2H, H-Het), 8.05 (s, 1H, H-Het), 8.13 (d, J = 8.9 Hz, 1H, H-Het). ^{13}C NMR (DMSO d_6): δ 102.0 (OCH_2O), 107.8, 109.0, 119.9, 122.5, 124.3, 126.2, 129.3, 130.0, 130.8, 131.3, 132.2, 132.9, 137.3, 146.9, 148.3, 148.6, 149.4, 156.13 (C_{arom}). IR (cm^{-1}): υ 3049, 2890, 1589, 1505, 1483, 1369, 1245, 1037, 827, 776, 700. MSD 360.0 (M^+).

Anal. Calcd. for $C_{22}H_{14}ClNO_2$: C, 73.44; H, 3.92; N, 3.89. Found: C, 73.65; H, 3.89; N, 3.93.

4.1.3.8. 2-(benzo[d][1,3]dioxol-5-yl)-6-chloro-4-(2-chlorophenyl)quinoline ***39***. Pale yellow solid; yield 55%, mp 166–168 °C, crystallized from EtOH. ^{1}H RMN (DMSO d_6): δ 6.14 (s, 2H, OCH_2O), 7.08 (d, J = 8.5 Hz, 1H, H—Ar), 7.30 (s, 1H, H_3C_6-OCH_2O), 7.47–7.50 (m, 3H, H—Ar), 7.72–7.82 (m, 2H, H—Ar), 7.93 (d, J = 6.3 Hz, 2H, H-Het), 8.12–8.30 (m, 2H-Het). ^{13}C NMR (DMSO d_6): δ 102.4 (OCH_2O), 107.7, 109.0, 120.4, 122.6, 124.1, 126.3, 128.1, 130.2, 131.0, 131.2, 131.5, 132.2, 132.6, 132.7, 136.0, 145.8, 146.5, 148.6, 149.5, 156.2 (C_{arom}). IR (cm^{-1}): υ 3086, 2879, 2776, 1602, 1472, 1246, 1036, 820, 759. MSD 394.0 (M^+).

Anal. Calcd. for $C_{22}H_{13}Cl_2NO_2$: C, 67.02; H, 3.32; N, 3.55. Found: C, 68.92; H, 3.36; N, 3.61.

4.1.3.9. 2-(benzo[d][1,3]dioxol-5-yl)-6-nitro-4-phenylquinoline ***40***. Pale yellow solid; yield 58%, mp 195–197 °C, crystallized from EtOH. ^{1}H NMR (DMSO d_6): δ 6.15 (s, 2H, OCH_2O), 7.09 (d, J = 8.1 Hz, 1H, $H_3C_6OCH_2O$), 7.57–7.70 (m, 5H, H-Ph), 7.95–8.02 (m, 2H, $H_3C_6OCH_2O$), 8.20 (s, 1H, H-Het), 8.26 (d, J = 9.2 Hz, 1H, H-Het), 8.47 (d, J = 9.2 Hz, 1H, H-Het), 8.64 (s, 1H, d, H-Het). ^{13}C NMR ($CDCl_3$): δ 102.2 (OCH_2O), 108.0, 109.1, 120.5, 122.8, 123.4, 123.6, 124.3, 130.2, 131.8, 132.3, 136.8, 145.1, 148.7, 150.1, 150.7, 150.9, 158.9 (C_{arom}). IR (cm^{-1}): υ 3082, 3049, 2901, 1592, 1506, 1484, 1339, 1038, 811, 703. MSD 371.0 (M^+).

Anal. Calcd. for $C_{22}H_{14}N_2O_4$: C, 71.35; H, 3.81; N, 7.56. Found: C, 71.30; H, 3.78; N, 7.60.

4.1.3.10. 2-(benzo[d][1,3]dioxol-5-yl)-4-(2-chlorophenyl)-6-nitroquinoline ***41***. Pale yellow solid; yield 55%, mp 259–260 °C, crystallized from EtOH. ^{1}H NMR (600 MHz, DMSO d_6): δ 6.10 (s, 2H, H_{24}), 6.98 (d, J = 8.2 Hz, 1H, H_{19}), 7.46 (dd, J = 1.5 Hz, J = 7.5 Hz, 1H, H_{12}), 7.51 (dt, J = 1.0 Hz, J = 7.5 Hz, 1H, H_{13}), 7.56 (dt, J = 1.5 Hz, J = 8.0 Hz, 1H, H_{14}), 7.66 (d, J = 8.8 Hz, 1H, H_{15}), 7.77 (dd, J = 1.6 Hz, J = 8.2 Hz, 1H, H_{18}), 7.85 (d, J = 1.6 Hz, 1H, H_{22}), 7.89 (s, 1H, H_9), 8.31 (d, J = 9.2 Hz, 1H, H_3), 8.44 (d, J = 2.4 Hz, 1H, H_6), 8.50 (dd, J = 2.4 Hz, J = 9.2 Hz, 1H, H_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 101.67 (OCH_2O), 108.0, 108.6, 121.0, 122.6, 122.7, 123.2, 124.7, 127.3, 130.3, 130.7, 131.3, 131.5, 132.7, 133.2, 135.5, 145.3, 148.4, 145.0, 150.7, 159.3 (C_{arom}). IR (cm^{-1}): υ 3083, 2894, 1601, 1496, 1453, 1337, 1245, 1031, 888, 815. MSD 404.0 (M^+).

Anal. Calcd. for $C_{22}H_{13}ClN_2O_4$: C, 65.28; H, 3.24; N, 6.92. Found: C, 65.33; H, 3.19; N, 6.89.

4.1.3.11. 6-chloro-2-(phenanthren-3-yl)-4-phenylquinoline ***42***. Yellow solid; yield 67%, mp 178–180 °C, crystallized from EtOH. ^{1}H RMN (600 MHz, $CDCl_3$): δ 7.59–7.68 (m, 6H), 7.72–7.75 (m, 2H),7.82 (m, 2H) 7.91–7.92 (m, 2H), 8.05 (d, J = 8.2 Hz, 1H), 8.08 (s, 1H, H-Het) 8.29 (d, J = 8.9 Hz, 1H), 8.46 (dd, J = 1.6 Hz; J = 8.2 Hz, 1H, H-Het), 8.91 (d, J = 8.2 Hz ,1H, H-Het), 9.55 (d, J = 1.1 Hz, 1H, H-Het). ^{13}C NMR (151 MHz, $CDCl_3$) δ 120.2, 122.1, 123.0, 124.6, 125.6, 126.6, 126.6, 126.8, 126.9, 128.0, 128.7, 128.8, 128.9, 129.2, 129.5, 129.5, 130.5, 130.6, 130.6, 131.8, 132.3, 132.3, 132.9, 137.1, 137.8, 147.4, 148.6, 157.1 (C_{arom}). IR (cm^{-1}): υ 3005, 2956, 1591, 1544, 1486, 1361, 1153, 849, 748, 705. MSD 416.0 (M^+).

Anal. Calcd. for $C_{29}H_{18}ClN$: C, 83.75; H, 4.36; N, 3.37. Found: C, 83.92; H, 4.39; N, 3.30.

4.1.3.12. 6-nitro-2-(phenanthren-3-yl)-4-phenylquinoline ***43***. Yellow solid; yield 50%, mp 235–237 °C, crystallized from EtOH. ^{1}H NMR ($CDCl_3$): δ 7.67 (s, 1H, H—Ar), 7.70–7.88 (m, 8H, H—Ar), 7.96 (d, J = 8.0 Hz, 1H, H-Het), 8.07 (d, J = 8.0 Hz, 1H, H-Het), 8.22 (s, 1H, H-Het), 8.43–8.57 (m, 3H, H—Ar), 8.90–8.93 (m, 2H, H—Ar), 9.62 (s, 1H, H-Het). ^{13}C NMR ($CDCl_3$): δ 120.9, 122.6, 122.9, 123.2, 124.9, 125.6, 126.5, 127.0, 128.6, 128.8, 129.2, 129.4, 129.5, 130.5, 131.8, 132.3, 133.4, 136.3, 137.0, 145.4, 151.4, 160.1 (C_{arom}). IR (cm^{-1}): υ 3049, 3022, 1590, 1552, 1482, 1336, 1079, 838, 748, 695. MSD 427.1 (M^+).

Anal. Calcd. for $C_{29}H_{18}N_2O_2$: C, 81.67; H, 4.25; N, 6.57. Found: C, 81.62; H, 4.28; N, 6.54.

4.1.4. General procedure for compounds ***44–45***

A mixture of the corresponding aniline (0.50–0.52 mL, 5.5 mmoles), piperonal (0.79 g, 5.25 mmoles), 3-acetylindole or acetophenone (0.87–0.66 g, 5.5 mmoles) with 0.15 mL of TFA placed in a 50 mL round-bottomed flask was subjected to MW irradiation at 400 W and 250 °C. After completion of the reaction (TLC) was proceed as described for **16–23**.

4.1.4.1. 2-(benzo[d][1,3]dioxol-5-yl)-4-phenyl-6-(trifluoromethyl)quinoline ***45***. White solid; yield 49%, mp 115–117 °C, crystallized from EtOH. ^{1}H RMN (600 MHz, $CDCl_3$): δ 6.04 (s, 2H, OCH_2O), 6.86 (d, J = 8.0 Hz, 1H, H—Ar), 7.14

(d, J = 7.8 Hz, 1H, H—Ar), 7.19 (s, 1H, H-Het), 7.39 (d, J = 15.6 Hz, 1H, H-Het), 7.52 (t, J = 7.6 Hz, 2H, Ph), 7.59 (t, J = 7.2 Hz, 2H, Ph), 7.76 (d, J = 15.6 Hz, 1H, H-Het), 8.02 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 101.6 (OCH_2O), 106.7, 108.7, 120.1, 125.2 (CF_3), 128.4, 128.6, 129.4, 132.6, 138.4, 144.7, 148.4 (C_{arom}), 149.93 (C_{arom}-CF_3). IR (cm^{-1}): υ 3036, 2922, 2785, 1660, 1590, 1503, 1450, 1253, 1018, 844, 777, 699, 598. MSD 392.0 (M^+).

Anal. Calcd. for $C_{23}H_{14}F_3NO_2$: C, 70.23; H, 3.59; N, 3.56. Found: C, 70.19; H, 3.62; N, 3.50.

4.2. In vitro activity against M. tuberculosis (Mtb)

4.2.1. Minimal inhibitory concentration (MIC)

The MIC of compound was determined by measuring bacterial growth after 5 d in the presence of test compounds. Compounds were prepared as 20-point two-fold serial dilutions in DMSO and diluted into 7H9-Tw-OADC medium in 96-well plates with a final DMSO concentration of 2%. The highest concentration of compound was 200 μM where compounds were soluble in DMSO at 10 mM. For compounds with limited solubility, the highest concentration was 50X less than the stock concentration e.g. 100 μM for 5 mM DMSO stock, 20 μM for 1 mM DMSO stock. Control compounds were prepared as 10-point two-fold dilution series. Each plate included assay controls for background (medium/DMSO only, no bacterial cells), zero growth (100 μM rifampicin) and maximum growth (DMSO only), as well as a rifampicin dose response curve. Plates were inoculated with *M. tuberculosis* and incubated for 5 days: growth was measured by OD590 and fluorescence (Ex 560/Em 590) using a BioTek™ Synergy 4 plate reader. Growth was calculated separately for OD590 and RFU. To calculate the MIC, the dose response curve was plotted as % growth and fitted to the Gompertz model using GraphPad Prism 5. The MIC was defined as the minimum concentration at which growth was completely inhibited and was calculated from the inflection point of the fitted curve to the lower asymptote (zero growth). In addition, dose response curves were generated using the Levenberg-Marquardt algorithm and the concentrations that resulted in 50% and 90% inhibition of growth were determined (IC_{50} and IC_{90} respectively).

4.2.2. Minimal bactericidal concentration (MBC)

M. tuberculosis was grown aerobically to logarithmic phase and inoculated into liquid medium containing four different compound concentrations with a final maximum concentration of 2% DMSO. For compounds with an MIC (from Task Group 1 assay), the concentrations selected were 10X MIC, 5X MIC, 1X MIC, and 0.25X MIC. For compounds with MIC > 20 μM, fixed concentrations of 200, 100, 20 and 5 μM were used (assuming solubility to 10 mM in DMSO). Cultures were exposed to compounds for 21 days and cell viability measured by enumerating colony forming units on agar plates on day 0, 7, 14 and 21. MICs were calculated as the average of the MIC derived from RFU and OD from Assay Group 1.

MBC was defined as the minimum concentration required to achieve a 2-log kill in 21 days. For compounds with >1-log kill, an assessment of time- and/or concentration-dependence was determined from the kill kinetics. DMSO was used as a positive control for growth.

4.2.3. Low-oxygen recovery assay (LORA)

Test compounds were prepared as 20-point two-fold serial dilutions in DMSO and diluted into DTA medium in 96-well plates with a final DMSO concentration of 2%. The highest concentration of compound was 200 μM where compounds were soluble in DMSO at 10 mM. For compounds with limited solubility, the highest concentration was 50X less than the stock concentration e.g. 100 μM for 5 mM DMSO stock, 20 μM for 1 mM DMSO stock. Control compounds were prepared as 10-point two-fold serial dilutions in DMSO and diluted into DTA medium in 96-well plates with a final DMSO concentration of 2%.

M. tuberculosis constitutively expressing the luxABCDE operon was inoculated into DTA medium in gas-impermeable glass tubes and incubated for 18 days to generate hypoxic conditions (Wayne model of hypoxia). At this point, bacteria are in a non-replicating state (NRP stage 2) induced by oxygen depletion.

4.2.4. Intracellular drug activity and cytotoxicity

Murine J774 macrophages were infected with a luminescent strain of H_{37}Rv (which constitutively expresses luxABCDE) at a multiplicity of infection of 1. After 18 h, extracellular bacteria were removed by washing and compound was added. Infected macrophages were incubated in the presence of compound for 4 days at 1X and 10X MIC (as determined in aerobic culture in liquid medium from Task 1). For compounds with MIC > 20 μM, fixed concentrations of 20 μM and 200 μM were used. Bacteria were harvested from macrophages by lysis with 0.1% SDS, inoculated into growth media and allowed to grow aerobically for 5 days, when the amount of bacteria present was determined by luminescence. All assays were conducted in triplicate; each assay included a positive control (4 μM isoniazid) and a negative control (2% DMSO). The intracellular activity was expressed as a log reduction of *M. tuberculosis* using the formula:

$$[\text{Log RLU Day 4 Compound}] - [\text{Log RLU Day 4 DMSO}]$$

As a control for each assay, the inoculum was plated into 96-well plates, grown for 5 days and luminescence measured; correlation of RLU and CFU was confirmed for each run (data provided as excel spreadsheet). The baseline of infection was determined by harvesting bacteria from macrophages at day 0 before compound addition and plating for CFU determination in triplicate.

The cytotoxicity of compounds was determined by measuring Vero cell viability growth after 2 d in the presence of test compounds. Compounds were prepared as 10-point three-fold serial dilutions in DMSO. Vero cells were cultured in DMEM containing high glucose and GlutaMAX™, 10% FBS, and 1x of Penicillin-Streptomycin solution. Cells were inoculated into assay plates and cultured for 24 h before compound dilutions were added to a final DMSO concentration of 1%. The highest concentration of compound tested was 100 μM where compounds were soluble in DMSO at 10 mM. For compounds with limited solubility, the highest concentration was 50X less than the stock concentration e.g. 100 μM for

5 mM DMSO stock, 20 μM for 1 mM DMSO stock. Each plate included staurosporine as a control.

4.3. QSAR study

The descriptors were from different classes such as autocorrelation descriptors [e.g., autocorrelation (charge)], chi indices descriptors (e.g., chi chain), electrotopological state index descriptors (e.g., atom type electrotopological state), BCUT descriptors, constitutional descriptors (e.g., weight, ring counts) and topological descriptors (e.g., Zagreb index, Wiener numbers). The standard data reduction technique of 'Principal Component Analysis' (PCA) was used to reduce the columns of descriptors to the principal components that contain as much of the original information as possible. The first three PCA vectors were added to the study table containing the binary representation of the activity of the molecules (Todeschini and Consonni, 2009).

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.arabjc.2018.10.003.

References

Ahmad, O.K., Medley, J.W., Coste, A., Movassaghi, M., 2012. Direct synthesis of azaheterocycles from n-aryl/vinyl amides. Synthesis of 4-(methylthio)-2-phenylquinazoline and 4-(4-methoxyphenyl)-2-phenylquinoline. Org. Synth. 89, 549–561. https://doi.org/10.15227/orgsyn.089.0549.

Aly, E.I., Abadi, A.H., 2004. Synthesis and antitubercular activity of 6-chloro (Unsubstituted)-2-methoxy-9-substituted acridine derivatives. Arch. Pharm. Res. 27, 713–719. https://doi.org/10.1007/BF02980137.

Anand, N., Koley, S., Ramulu, B.J., Shankar Singh, M., 2015. Metal-free aerobic one-pot synthesis of substituted/annulated quinolines from alcohols via indirect Friedländer annulation. Org. Biomol. Chem. 13, 9570–9574. https://doi.org/10.1039/C5OB01422K.

Andries, K., Verhasselt, P., Guillemont, J., Göhlmann, H.W.H., Neefs, J.M., Winkler, H., et al, 2005. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. Science 307, 223–227. https://doi.org/10.1126/science.1106753.

Beyer, C., 1886. Über α-γ-dimethylchinolin und die synthese des cincholepidins und des γ-phenylchinaldins. J. Prakt. Chem. 33, 393–425. https://doi.org/10.1002/prac.18860330136.

Buu-Hoï, N.P., Cagniant, P., 1943a. Des Quinoléines Substituées II. Synthèse de nouvelles 2-arylquinoléines. Rec. Trav. Chim. Pays-Bas 62, 713–718. https://doi.org/10.1002/recl.19430621102; Beil. XXII, 523.

Buu-Hoï, N.P., Cagniant, P., 1943b. Des Quinoléines Substituées. I: Synthèse des 2. et 3. (α-quinoléyl)-phénanthrènes. Rec. Trav. Chim. Pays-Bas 62, 519–522. https://doi.org/10.1002/recl.19430620805.

Buu-Hoï, N.P., 1949. La p-hydroxypropiophénone, ses analogues et leurs dérivés. Rec. Trav. Chim. Pays-Bas 68, 759–780. https://doi.org/10.1002/recl.19490680811.

Casal, J.J., Asís, S.E., 2017. Natural and synthetic quinoline derivatives as *anti*-tuberculosis agents. Austin Tuberc. Res. Treat. 2 (1).

Chen, W.C., Lin, C.C., Kavala, V., Kuo, C.W., Huang, C.Y., Yao, C. F., 2015. Syntheses of 4-indolylquinoline derivatives via reductive cyclization of indolylnitrochalcone derivatives by Fe/HCl. Molecules 20, 22499–22519. https://doi.org/10.3390/molecules201219862.

Eaton, P.E., Carlson, G.R., Lee, J.T., 1973. Phosphorus pentoxide-methansulfonic acid. A convenient alternative to polyphosphoric acid. J. Org. Chem. 38, 4071–4073. https://doi.org/10.1021/jo00987a028.

Enugala, R., Nuvvula, S., Kotra, V., Varala, R., Adapa, S.R., 2008. Green approach for the efficient synthesis of quinolines promoted by citric acid. Heterocycles 75, 2523–2533. https://doi.org/10.3987/COM-08-11405.

Eswaran, S., Adhikari, A.V., Chowdhury, I.H., Pal, N.K., Thomas, K. D., 2010. New quinoline derivatives: synthesis and investigation of antibacterial and antituberculosis properties. Eur. J. Med. Chem. 45, 3374–3383. https://doi.org/10.1016/j.ejmech.2010.04.022.

Fournet, A., Ferreira, M.E., Rojas De Arias, A., Torres De Ortiz, S., Fuentes, S., Nakayama, H., Schinini, A., Hocquemiller, R., 1996. *In vivo* efficacy of oral and intralesional administration of 2-substituted quinolines in experimental treatment of new world cutaneous leishmaniasis caused by *Leishmania amazonensis*. Antimicrob Agents Chemother. 40, 2447–2451 http://aac.asm.org/content/40/11/2447.full.pdf+htm.

Gopi, P., Sarveswari, S., 2017. Effective water mediated green synthesis of polysubstituted quinolines without energy expenditure. Monats. Chem. 148, 1043–1049. https://doi.org/10.1007/s00706-016-1826-3.

Gopinath, V.S., Rao, M., Shivahare, R., Vishwakarma, P., Ghose, S., Pradhan, A., Hindupur, R., Das Sarma, K., Gupta, S., Puri, S.K., Launay, D., Martin, D., 2014. Design, synthesis, ADME characterization and antileishmanial evaluation of novel substituted quinoline analogs. Bioorg. Med. Chem. Lett. 24, 2046–2052. https://doi.org/10.1016/j.bmcl.2014.03.065.

Jain, R., Vaitilingam, B., Nayyar, A., Palde, P., 2003. Substituted 4-methylquinolines as a new class of *anti*-tuberculosis agents. Bioorg. Med. Chem. Lett. 13, 1051–1054. https://doi.org/10.1016/S0960-894X(03)00074-X.

Kobayashi, K., Yoneda, K., Miyamoto, K., Morikawa, O., Konishi, H., 2004. A convenient synthesis of quinolines by reactions of *o*-isocyano-*β*-methoxystyrenes with nucleophiles. Tetrahedron 60, 11639–11645. https://doi.org/10.1016/j.tet.2004.09.069.

Li, H., Wang, C., Huang, H., Xu, X., Li, Y., 2011. Silver-catalyzed cascade reaction of *o*-aminoaryl compounds with alkynes: an aniline mediated synthesis of 2-substituted quinolines. Tetrahedron Lett. 52, 1108–1111. https://doi.org/10.1016/j.tetlet.2010.12.102.

Liberto, N.A., Baptista Simões, J., de Paiva Silva, S., da Silva, C.J., Modolo, L.V., de Fátima, Â., Silva, L.M., Derita, M., Zacchino, S., Portilla Zuñiga, O.M., Romanelli, G.P., Fernandes, S.A., 2017. Quinolines: microwave-assisted synthesis and their antifungal, anticancer and radical scavenger properties. Bioorg. Med. Chem. 25, 1153–1162. https://doi.org/10.1016/j.bmc.2016.12.023.

Metallidis, S., Nikolaidis, J., Lazaraki, G., Koumentaki, E., Gogou, V., Topsis, D., Nikolaidis, P., Charokopos, N., Theodoridis, G., 2007. Int. J. Antimicrobial Agents 29, 738–748. https://doi.org/10.1016/j.ijantimicag.2007.01.012.

Muscia, G.C., Bollini, M., Carnevale, J.P., Bruno, A.M., Asís, S.E., 2006. Microwave-assisted Friedländer synthesis of quinolines derivatives as potential antiparasitic agents. Tet. Lett. 47, 8811–8815. https://doi.org/10.1016/j.tetlet.2006.10.073.

Muscia, G.C., Carnevale, J.P., Bollini, M., Asís, S.E., 2008. Microwave-assisted Döbner synthesis of 2-phenylquinoline-4-carboxylic

acids and their antiparasitic activities. J. Heterocyclic Chem. 45, 611–614. https://doi.org/10.1002/jhet.5570450251.

Muscia, G.C., Cazorla, S.I., Frank, F.M., Borosky, G.L., Buldain, G. Y., Asís, S.E., Malchiodi, E.L., 2011. Synthesis, trypanocidal activity and molecular modeling studies of 2-alkylaminomethylquinoline derivatives. Eur. J. Med. Chem. 46, 3696–3703. https://doi.org/10.1016/j.ejmech.2011.05.035.

Muscia, G.C., Buldain, G.Y., Asís, S.E., 2014. Design, synthesis and evaluation of acridine and fused-quinoline derivatives as potential *anti*-tuberculosis agents. Eur. J. Med. Chem. 73, 243–249. https://doi.org/10.1016/j.ejmech.2013.12.013.

Muscia, G.C., Asís, S.E., Buldain, G.Y., 2017. Microwave-assisted synthesis of 2-styrylquinoline-4-carboxylic acids as antitubercular agents. Med. Chem. 13, 448–452. https://doi.org/10.2174/1573406412666160901102710.

NIH/NIAID Task Order A01 Contract HHSN272201100012I. Task Order A08 – "in vitro characterization of anti-mycobacterial activity". Contract No. HHSN272201100009I / HHSN27200001 A08.

Palimkar, S.S., Siddiqui, S.A., Rajgopal, T.D., Lahoti, J., Srinivasan, K.V., 2003. Ionic liquid-promoted regiospecific Friedländer annulation: novel synthesis of Quinolines and fused polycyclic Quinolines. J. Org. Chem. 68, 9371–9378. https://doi.org/10.1021/jo035153u.

Patel, S.R., Gangwal, R., Sangamwar, A.T., Jain, R., 2014. Synthesis, biological evaluation and 3D-QSAR study of hydrazide, semicarbazide and thiosemicarbazide derivatives of 4-(adamantan-1-yl) quinoline as *anti*-tuberculosis agents. Eur J. Med. Chem. 85, 255–267. https://doi.org/10.1016/j.ejmech.2014.07.100.

Patel, S.R., Gangwal, R., Sangamwar, A.T., Jain, R., 2015. Synthesis, biological evaluation and 3D QSAR study of 2,4-disubstituted quinolines as *anti*-tuberculosis agents. Eur. J. Med. Chem. 93, 511–522. https://doi.org/10.1016/j.ejmech.2015.02.034.

Pfitzinger, W.J., 1886. Chinolin Derivate aus Isatinsäure. Prakt. Chem. 33, 100. https://doi.org/10.1002/prac.18850330110.

Prasad Korivi, R., Cheng, C., 2006. Nickel-catalyzed cyclization of 2-iodoanilines with aroylalkynes: an efficient route for quinoline derivatives. J. Org. Chem. 71, 7079–7081. https://doi.org/10.1021/jo060800d.

Rehan, M., Hazra, G., Ghorai, P., 2015. Synthesis of polysubstituted quinolines via transition-metal-free oxidative cycloisomerization of o-cinnamylanilines. Org. Lett. 17, 1668–1671. https://doi.org/10.1021/acs.orglett.5b00419.

Rustomjee, R., Diacon, A.H., Allen, J., Venter, A., Reddy, C., Patientia, R.F., et al, 2008. Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis. Antimicrob. Agents Chemother. 52, 2831–2835. https://doi.org/10.1128/AAC.01204-07.

Tang, J., Wang, L., Mao, D., Wang, W., Zhang, L., Wu, S., Xie, Y., 2011. Ytterbium pentafluorobenzoate as a novel fluorous Lewis acid catalyst in the synthesis of 2,4-disubstituted quinolines. Tetrahedron 67, 8465–8469. https://doi.org/10.1016/j.tet.2011.09.004.

Tanwar, B., Kumar, A., Yogeeswari, P., Sriram, D., Chakraborti, K., 2016. Design, development of new synthetic methodology, and biological evaluation of substituted quinolines as new anti-tubercular leads. Bioorg. Med. Chem. Lett. 26, 5960–5966. https://doi.org/10.1016/j.bmcl.2016.10.082.

Todeschini, R., Consonni, V., 2009. Molecular Descriptors for Chemoinformatics 27–37. Wiley-VCH, Weinheim.

Tsatsas, G., Delaby, R., Lusinchi, X., 1955. Synthetic preparation of some 2-[3,4-(dialkylmethylenedioxy)phenyl]-4-quinolinecarboxylic acids and their derivs. Chimika Chronika 20, 148–150.

Tuberculosis Fact sheet. Reviewed January, 2018. http://www.who.int/mediacentre/factsheets/fs104/en/. (Accessed February 2018).

Walter, H., 1998. The use of 2-vinylanilines in the synthesis of indole- and quinoline-derivatives. J. Prakt. Chem. 340, 309–314. https://doi.org/10.1002/prac.19983400404.

Xu, X., Liu, W., Wang, Z., Feng, Y., Yan, Y., Zhang, X., 2016. Silver-catalyzed one-step synthesis of multiply substituted Quinolines. Tetrahedron Lett. 57, 226–229. https://doi.org/10.1016/j.tetlet.2015.12.028.

Zhang, L., Wu, B., Zhou, Y., Xia, J., Zhou, S., Wang, S., 2013. Rare-earth metal chlorides catalyzed one-pot syntheses of quinolines under solvent-free microwave irradiation conditions. Chin. J. Chem. 31, 465–471. https://doi.org/10.1002/cjoc.201300047.